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Novel Human Histamine H_3 Receptor Antagonists

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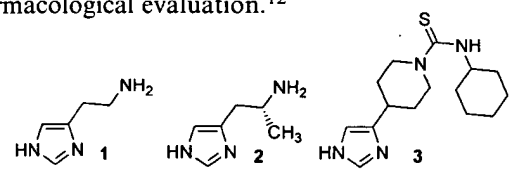
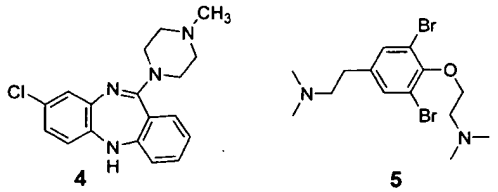
Abstract—High throughput screening, using the recombinant human H_3 receptor, was used to identify novel histamine H_3 receptor antagonists. Evaluation of the lead compounds ultimately afforded potent, selective, orally bioavailable compounds (e.g., **38**) with favorable blood–brain barrier penetration.

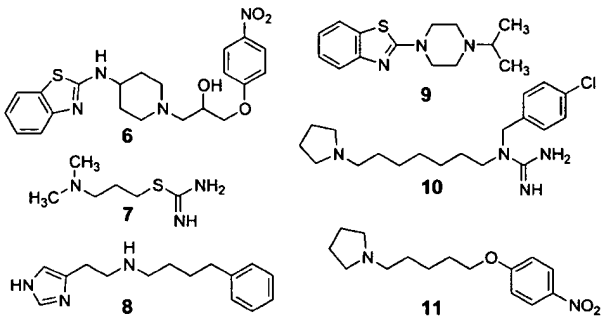
The monoamine histamine (**1**) exerts a physiological effect via four distinct G-protein coupled receptors. Thus histamine plays a role, via the H_1 receptor, in immediate hypersensitivity reactions upon IgE mediated release from mast cells.[1,2] Histamine is also an important regulator of gastric acid secretion through its action upon H_2 receptors expressed in parietal cells.[3] The third histamine receptor (H_3) identified in 1983, was first described as a pre- and postsynaptic autoreceptor in the brain[4] and subsequently as a presynaptic heteroreceptor on non-histamine containing neurons in both the central and peripheral nervous system.[5] Recently, a fourth histamine receptor (H_4) was described with an expression profile that suggests a role in immune function.[6–10] Our interests relate to ligands for the histamine H_3 receptor, in particular histamine H_3 receptor antagonists, and follows from the successful cloning of the human H_3 receptor.[11] Histamine H_3 ligands are postulated to have a range of therapeutic applications and both H_3 agonists (e.g., *R*-α-methylhistamine **2**) and antagonists (e.g., thioperamide **3**) have undergone pharmacological evaluation.[12]



Until recently, a common feature of these molecules is their retention of the imidazole nucleus present in the natural ligand. This results in compounds with poor blood–brain barrier (BBB) penetration[13] and metabolic liabilities associated with the imidazole ring.[14] Although compounds such as clozapine[15] **4** and the marine natural product aplysamine[16] **5** were reported to be H_3 antagonists, earlier efforts to identify imidazole replacements were disappointing.[17]



Only very recently have several groups described series of potent non-imidazole based histamine H_3 antagonists. Thus these groups have used low affinity H_3 ligands sabeluzole[18] **6**, dimaprit[19] **7** and N^{α}-(4-phenylbutyl)histamine[20] **8** to obtain antagonists **9**, **10**, and **11**, respectively.



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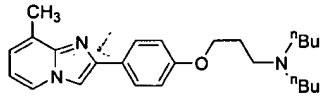
Recognizing the deficiencies of the existing imidazole based ligands and the need to identify additional non-imidazole small molecule lead compounds, we undertook a high throughput screening (HTS) approach using the recombinant human receptor. Thus, HTS was initiated with the objective of finding small molecule leads that could ultimately afford compounds that were orally bioavailable and had good BBB penetration. A secondary objective was to evaluate a H_3 antagonist in a range of central nervous system (CNS) disorders.

Results

To our satisfaction, HTS afforded several lead series with good affinity for the human H_3 receptor including a series of 2-phenyl-imidazo[1,2-*a*]pyridines. These compounds were first prepared as calcium channel blockers and subsequently found to exhibit local anesthetic properties independent of their calcium blocking activity (e.g., RWJ-20085, **12**).[21,22] Thus, **12** was found to be a weak histamine H_3 receptor ligand ($K_i = 4$ μM).



12

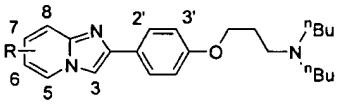
Screening analogues of **12** retaining the di-*n*-butylamino terminus, which had been essential for local anesthetic activity, indicated that a range of substituents were tolerated in the 2-phenyl-imidazo[1,2-*a*]pyridine fragment with minimal effect on potency (Table 1).

However, when we turned our attention to analogues in which the size of the terminal amino group was reduced a dramatic increase in potency was observed. In particular, analogues containing cyclic amines provided significantly more potent compounds (Table 2).

Thus these early screening results quickly demonstrated the favorable effect of a piperidinylpropyl side chain and so a limited number of substitutions in the 2-phenyl-imidazopyridine nucleus were examined whilst maintaining the piperidinylpropyl side chain. This indicated that small alkyl groups were tolerated in the imidazopyridine nucleus (Table 3). Simultaneously we observed that the cyclic amine could be piperidine, pyrrolidine or cycloheptylamine (Table 4).

At this juncture, we selected the 7-methylimidazopyridine analogue **38** for more detailed evaluation. The 7-methyl substituent was retained since it was known to reduce both calcium channel affinity and local anesthetic activity in the original series of compounds.[21] Syntheses of the compounds were accomplished

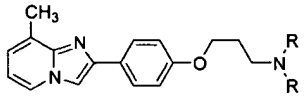
Table 1. Imidazopyridine and aryl ring substituents, di-*n*-butylamino terminus



No.	R	K_i (nM)	No.	R	K_i (nM)
12	8-CH_3	2700	**20**	6,8-di-Br	4800
13	H	1300	**21**	8-$PhCH_2O$	2400
14	7-CH_3	1100	**22**	6-Br	2900
15	6-CH_3	1900	**23**	8-OH	1500
16	5-CH_3	2100	**24**	2′,8-di-CH_3	4200
17	3,8-di-CH_3	870	**25**	3′,8-di-CH_3	8000
18	5,7-di-CH_3	2000	**26**	3′-OCH_3, 8-CH_3	1700
19	8-NO_2	11,000	**27**	3′,5′-di-OCH_3, 8-CH_3	3300

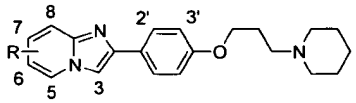
K_i values are the mean of two to six determinations and were determined in house and calculated according to Cheng and Prusoff[23] where $K_i = IC_{50}/(1 + [S]/K_d)$ where $[S] = 0.8$ nM and $K_d = 0.8$ nM for [^{3}H]-*N*-methylhistamine.

Table 2. Amino group substitutions



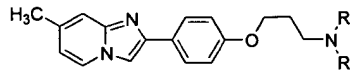
No.	NR_2	K_i (nM)	No.	NR_2	K_i (nM)
28	N-(^{n}C_5H_{11})$_2$	7900	**34**		1000
12	N-(^{n}C_4H_9)$_2$	2700			
30	N-(^{n}C_3H_7)$_2$	43	**35**		80
31	N-(CH_3)$_2$	13			
32	N-(CH(CH_3)Ph)$_2$	4000	**36**		3
33	$NHCH_2Ph$	5400			

Table 3. Imidazopyridine and aryl ring substituents, piperidino terminus

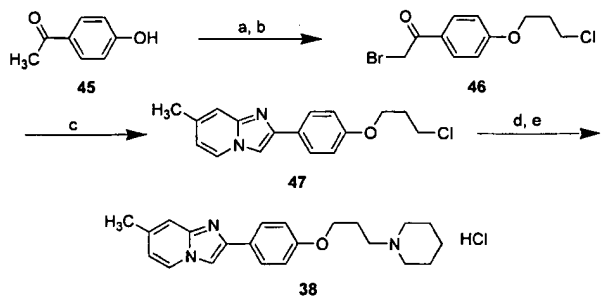


No.	R	K_i (nM)	No.	R	K_i (nM)
37	H	6	**40**	2′,7-di-CH_3	2
36	8-CH_3	3	**41**	2′F, 7-CH_3	10
38	7-CH_3	2	**42**	3′-OCH_3, 7-CH_3	69
39	3′-CH_3	28			

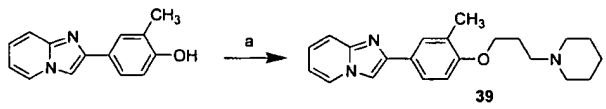
Table 4. Alkylamine ring size



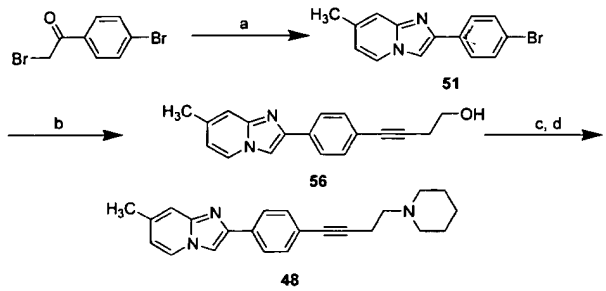
No.	$-NR_2$	K_i (nM)
38		2
43		5
44		6



Scheme 1. Reagents and conditions: (a) K_2CO_3, 1-bromo-3-chloropropane, acetone, reflux, 18 h, 98%; (b) Br_2, Et_2O, 18 h, 98%; (c) 2-amino-4-picoline, EtOH, 73 °C, 2 h, 63%; (d) piperidine, 100 °C, 1.5 h, 90%; (e) MeOH, 2M HCl/Et_2O, 100%.



Scheme 2. Reagents and conditions: (a) 3-piperidinyl propan-1-ol, DEAD, polymer bound PPh_3, THF, 20 h, 25%.

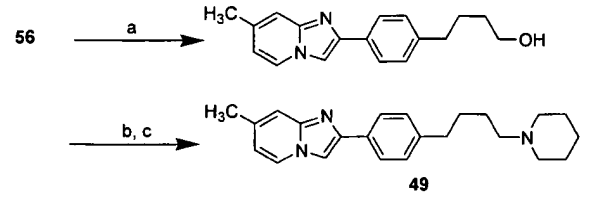


Scheme 3. Reagents and conditions: (a) 2-amino-4-picoline, EtOH, reflux, 18 h, 58%; (b) 3-butyn-1ol, CuI, NEt_3, $Pd(PPh_3)_4$, CH_3CN, reflux, 18 h, 56%; (c) MsCl, pyridine, CH_2Cl_2, 80%; (d) piperidine, K_2CO_3, CH_3CN, reflux, 18 h, 97%.

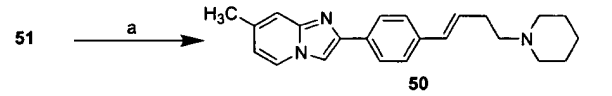
according to the procedure outlined in Scheme 1 for the preparation of **38**. Thus an appropriately substituted 4-hydroxyacetophenone (**45**) was alkylated with 1-bromo-3-chloropropane and brominated to give **46**. Condensation of **46** with a 2-aminopicoline gave **47**, which was treated with an amine to afford **38**.

The aminoalkyl side chain could also be introduced via a Mitsunobu reaction as shown for the preparation of **39** (Scheme 2).

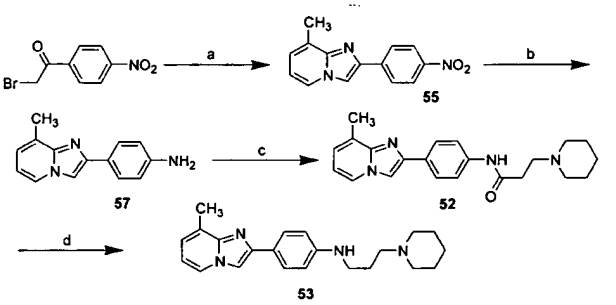
In parallel to the detailed biological evaluation of **38** alternatives to the ether linkage present in **38** were explored (Table 5). The syntheses of these analogues were accomplished as shown in Schemes 3–7. Thus the carbon linked analogues **48–50** were prepared from the 2-(4-bromophenyl)-imidazo[1,2-*a*]pyridine **51** via either a Sonogashira coupling (Schemes 3 and 4) or a Heck coupling reaction (Scheme 5). The nitrogen linked analogues, **52–54** were prepared from the 2-(4-nitrophenyl) imidazo[1,2-*a*]pyridine **55** (Scheme 6). The intermediates **51** and **55** were in turn prepared via condensation of an appropriately substituted acetophenone with a 2-aminopicoline.



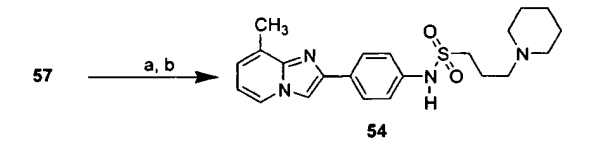
Scheme 4. Reagents and conditions: (a) 5% Pd–$BaSO_4$, H_2, EtOH, 4.5 h, 100%; (b) MsCl, NEt_3, CH_2Cl_2, 18 h, 100%; (d) piperidine, K_2CO_3, CH_3CN, reflux, 18 h, 48%.



Scheme 5. Reagents and conditions: (a) 1-but-3-enylpiperidine, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 150 °C, 20 h, 14%.

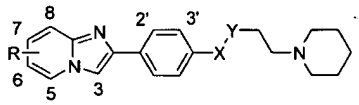


Scheme 6. Reagents and conditions: (a) 2-amino-3-picoline, EtOH, reflux, 1.5 h, 22%; (b) cyclohexadiene, Pd/C, EtOH, reflux, 2 h, 50%; (c) 1-piperidinepropionic acid, EDAC, HOBT, $^iPr_2NEt$, DMF, 18 h, 24%; (d) 2M BH_3/DMS, $PhCH_3$, reflux, 18 h, 51%.



Scheme 7. Reagents and conditions: (a) 3-chloropropanesulfonyl chloride, NEt_3, DMF, 1.5 h, 66%; (b) piperidine, 100 °C, 18 h, 88%.

Table 5. Linker variations



No. R = 7-CH_3	X–Y	K_i (nM)	No. R = 8-CH_3	X–Y	K_i (nM)
38	OCH_2	2	**37**	OCH_2	6
48	C≡C	7	**52**	NH(CO)	300
49	CH_2CH_2	17	**53**	$NHCH_2$	15
50	CH=CH *trans/cis* 9:1	22	**54**	$NHSO_2CH_2$	500

Although these studies were not exhaustive, they demonstrated that the ether linkage could be replaced with a carbon or an amine linkage without significant loss of affinity. However the amide and sulfonamide analogues **52** and **54** were considerably less active.

Biological Results and Discussion

Following the successful identification of small molecule histamine H_3 ligands a more detailed biological evaluation was undertaken. Thus in vitro **38** demonstrated high affinity for the human H_3 receptor ($K_i = 2$ nM) with slightly reduced affinity for the recombinant rat H_3 receptor ($K_i = 10$–20 nM). In addition **38** exhibited approximately 1000-fold selectivity over the H_1, H_2, and H_4 receptors. Broad screening against a panel of over 50 receptor targets representing the major classes of biogenic amine and neuropeptide receptors, ion channels and neurotransmitter transporters indicated affinities greater than $K_i = 1$ μM. Functional activity versus the human H_3 receptor was determined using SKNMC cells stably transfected with the human H_3 receptor. These compounds, exemplified by **38**, produced a rightward shift in the histamine dose–response curve yielding a $pA_2 = 8.69$. The corresponding rat pA_2 was weaker at 8.33. In vivo blood–brain barrier penetration (BBB) was measured following peripheral administration. Thus, **38** was administered (10 mg/kg ip) to rats which afforded a brain $C_{max} = 10.8 \pm 0.8$ μM on a weight/volume basis. Brain receptor occupancy was determined via ex-vivo autoradiography and **38** exhibited an $ED_{50} = 0.2$ mg/kg sc using [^{3}H]-*R*-α-methylhistamine to define sites not blocked by the test compound. In the same protocol thioperamide (**3**) had an $ED_{50} = 2$ mg/kg. Single dose rat pharmacokinetics confirmed that **38** had good oral bioavailability (57%) with a moderate half life ($t_{1/2} = 5.2 \pm 1.2$ h). Thus, with the objective of identifying small molecule H_3 antagonists having good oral bioavailability and favorable BBB penetration achieved, pharmacological evaluation was initiated in a range of behavioral and cognitive models, details of which will be reported elsewhere.

In summary, proceeding from the cloning of the human H_3 receptor and initiation of a HTS screen a series of novel histamine H_3 ligands were identified. The SARs for the leads were promptly delineated to obtain potent, orally bioavailable, brain penetrating compounds that will aid in the elucidation of the role of central histamine H_3 receptors and determine the therapeutic potential of H_3 receptor antagonists.

Acknowledgements

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